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EXAMINER

CROUCH, DEBORAH

ART UNIT PAPER NUMBER

1632

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/918,702

**Applicant(s)**

BENVENISTY, NISSIM

**Examiner**

Deborah Crouch, Ph.D.

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on 27 September 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 8-16 and 48-69 is/are pending in the application.
- 4a) Of the above claim(s) 49,53,56,58,61,63,64,66 and 68 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 8-16, 48, 50-52, 54, 55, 57, 59, 60, 62, 65, 67 and 69 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: \_\_\_\_\_.

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Applicant's arguments filed September 27, 2004 have been fully considered but they are not persuasive. The amendment has been entered. The declaration by Nissam Benvensity has been considered but is not persuasive. Claims 8-16 and 48-69 are pending. Claims 1-16, 48, 50-52, 54, 55, 57, 59, 60 62, 65, 67 and 69 are examined in this office action. Claims 49, 53, 56, 58, 61, 63, 64, 66 and 68 are withdrawn from examination for reasons presented in the office action mailed June 1, 2004.

Applicant is correct in their assessment that claim 8 is a linking claim. The allowance of these claims will be considered at the time of the allowance of claim 8.

Applicant's amendment to claim 10 has overcome the rejection made in the previous office action as lacking enablement under 35 U.S.C. 112, first paragraph.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 8, 9 11, 12, 60 and 65 remain rejected under 35 U.S.C. 103(a) as being unpatentable over in Thomson et al (1998) Science 282, 1145-1147 in view of Shamblott et (1998) Proc. Natl. Acad. Sci. (USA) 95, 13726-13731 and further in view further in view of Yuen et al. (1998) Blood 91, 3202-3209 for reasons presented in the office action mailed June 1, 2004.

Thomson teaches human ES cells that retain the ability to form all three embryonic germ layers (page 1146, col. 1, parag. 2, lines 1-3).

Shamblott teaches the production of human EB's from human primordial germ cells (PGC's), cultured with or without LIF (page 13729, col. 1-2, bridg. parag). Primordial germ cells (PGC's) are the source for embryonic germ (EG) cells, and in mice is a cell that shares

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pluripotent characteristics with mouse ES cells (page 13726, col. 1, lines 1-5). Shamblott also teaches that human EG cells have several characteristics in common with mouse ES and EG cells, especially the ability to develop into all three germ layers (page 13726, col. 2, parag. 1 and page 13729, col. 2, parag. 5, lines 1-11).

Yuen teaches the production of embryoid bodies (EB's) in suspension from mouse ES cells (page 3203, col. 1, lines 3-7). After aggregation, the EB's were dissociated with trypsin to produce embryonic cells which were then cultured on an extracellular matrix, methylcellulose (page 3203, col. 1, parag. 1, lines 1-3). The embryonic cells/methylcellulose cultures were grown in the presence of transferrin, bFGF and Epo, and resulting primitive erythroid cells were culture in media containing several interleukins, IL-3, -11 and -6, all of which are growth factors directing differentiation to hematopoietic stem cells (page 3203, col.1, parag. 1, lines 4-10 and parag. 2, lines 1-5). Erythroid cells, a type of blood cells, arise from the mesoderm.

Therefore at the time of the present invention, it would have been obvious to the ordinary artisan to produce human EB's from human ES cells as taught by Thomson using the methodology of Shamblott, and then, following the methodology of Yuen for mouse EB's, produce a culture of embryonic cells by dissociating human EB's, and culture the embryonic cells in the presence of transferrin, bFGF, and EPO and IL3 to observe the formation of primitive erythroid cells. Motivation can be found in Thomson teaching that human ES cells will offer insights into developmental events that cannot be studied in a human embryo but which have important consequences in birth defects, infertility and pregnancy loss (page 1146, col. 1, parag. 3, lines 1-6). Thus, at the time of filing, the ordinary artisan would have had sufficient teaching, suggestion and motivation to reach the claimed invention to develop an in vitro method studying human erythrocyte differentiation from ES cells.

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Applicant should be aware that the phrase in claim 8, "for differentiating in the presence of at least one exogenous factor for an effective period of time" is regarded as an intended use for the cells, and not, necessarily, part of the presently claimed invention. There is no limitation in the claims that the embryonic cells produced by dissociating embryoid bodies are themselves, specifically, cultured in the presence of an exogenous factor. Thus Yuen teaching the culture of EB's with exogenous factors and then observing the formation of erythroid cells reads on the claimed invention.

Claims 8-12, 14-16, 48, 51 and 52 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson et al (1998) Science 282, 1145-1147 in view of Shamblott et (1998) Proc. Natl. Acad. Sci (USA) 95, 13726-13731 and further in view of Bain et al (1995) Devel. Biol. 168, 342-357 for reasons presented in the office action mailed June 1, 2004.

Thomson teaches human ES cells that retain the ability to form all three embryonic germ layers (page 1146, col. 1, parag. 2, lines 1-3).

Shamblott teaches the production of human EB's from human primordial germ cells (PGC's), cultured with or without LIF (page 13729, col. 1-2, bridg. parag). Primordial germ cells (PGC's) are the source for embryonic germ (EG) cells, and in mice is a cell that shares pluripotent characteristics with mouse ES cells (page 13726, col. 1, lines 1-5). Shamblott also teaches that human EG cells have several characteristics in common with mouse ES and EG cells, especially the ability to develop into all three germ layers (page 13726. col. 2, parag. 1 and page 13729, col. 2, parag. 5, lines 1-11).

Bain teaches the production of EB's in suspension by the aggregation of mouse ES cells (page 343, col.2, parag. 2, lines 23-26). EB's were cultured in median comprising retinoic acid (RA) (page). EB's were then dissociated with trypsin and plated on laminin-coated dishes (page 344, col. 1, lines 3-6). The monolayer cells, plated on laminin coated

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plates, developed into neuron-like cells having neuritic processes (page 347, col. 1, lines 3-4). Neurons, like other brain cells are of ectodermal origin.

Therefore at the time of the present invention, it would have been obvious to the ordinary artisan to produce human EB's from human ES cells as taught by Thomson using the methodology of Shambloott, and then following the methodology of Bain for mouse EB's, culture the human EB's in the presence of retinoic acid, subsequently dissociate the human EB's and plate the embryonic cells thereby produced on a laminin coated plate to produce a monolayer of embryonic cells to observe neuron-like cells with neuritic processes.

Motivation can be found in Thomson teaching that human ES cells will offer insights into developmental events that cannot be studied in a human embryo but which have important consequences in birth defects, infertility and pregnancy loss (page 1146, col. 1, parag. 3, lines 1-6). Thus, at the time of filing, the ordinary artisan would have had sufficient teaching, suggestion and motivation to reach the claimed invention to develop an in vitro system to observe neuronal cells differentiation from human ES cells.

Claims 8, 11, 13, 48, 51 and 52 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson et al (1998) Science 282, 1145-1147 in view of Shambloott et (1998) Proc. Natl. Acad. Sci (USA) 95, 13726-13731 and further in view of Bain et al (1995) Devel. Biol. 168, 342-357 and Wobus et al (1988) Biomed. Biochim. Acta 47, 965-973 for reasons presented in the office action mailed June 1, 2004.

Thomson teaches human ES cells that retain the ability to form all three embryonic germ layers (page 1146, col. 1, parag. 2, lines 1-3).

Shambloott teaches the production of human EB's from human primordial germ cells (PGC's), cultured with or without LIF (page 13729, col. 1-2, bridg. parag). Primordial germ cells (PGC's) are the source for embryonic germ (EG) cells, and in mice is a cell that shares pluripotent characteristics with mouse ES cells (page 13726, col. 1, lines 1-5). Shambloott

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also teaches that human EG cells have several characteristics in common with mouse ES and EG cells, especially the ability to develop into all three germ layers (page 13726, col. 2, parag. 1 and page 13729, col. 2, parag. 5, lines 1-11).

Bain teaches the production of EB's in suspension by the aggregation of mouse ES cells (page 343, col.2, parag. 2, lines 23-26). EB's were cultured in median comprising retinoic acid (RA) (page). EB's were then dissociated with trypsin and plated on laminin-coated dishes (page 344, col. 1, lines 3-6). The monolayer cells, plated on laminin coated plates, developed into neuron-like cells having neuritic processes (page 347, col. 1, lines 3-4).

Wobus teaches the production of neuron-like cells in culture when mouse EB's are cultured in the presence of nerve growth factor (NGF) (page 968, line 9 to page 969, line 2). Wobus states that NGF is important for the survival of neurons during embryonic development, for growth of sensory and sympathetic ganglia and for differentiation and maintenance of specific neuronal function (page 965, parag. 2, lines 5-8).

Therefore at the time of the present invention, it would have been obvious to the ordinary artisan to produce human EB's from human ES cells as taught by Thomson using the methodology of Shambloott, and then following the methodology of Bain for mouse EB's, culture the human EB's in the presence of NGF as taught by Wobus, subsequently dissociate the human EB's and plate the embryonic cells thereby produced on a laminin coated plate to produce a monolayer of embryonic cells to observe neuron-like cells with neuritic processes. Motivation can be found in Thomson teaching that human ES cells will offer insights into developmental events that cannot be studied in a human embryo but which have important consequences in birth defects, infertility and pregnancy loss (page 1146, col. 1, parag. 3, lines 1-6). Additional motivation can be found in Wobus stating the results disclosed establish an experimental cell model to study the effect on differentiation of stem cells

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(page 970, parag. 2). Thus, at the time of filing, the ordinary artisan would have had sufficient teaching, suggestion and motivation to reach the claimed invention to develop an in vitro system to study the role of NGF on human neuronal cell differentiation from ES cells.

Claim 55 is rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson et al (1998) Science 282, 1145-1147 in view of Shambloott et (1998) Proc. Natl. Acad. Sci (USA) 95, 13726-13731 and further in view of Bain et al (1995) Devel. Biol. 168, 342-357 and Wobus et al (1988) Biomed. Biochim. Acta 47, 965-973.

Thomson teaches human ES cells that retain the ability to form all three embryonic germ layers (page 1146, col. 1, parag. 2, lines 1-3).

Shambloott teaches the production of human EB's from human primordial germ cells (PGC's), cultured with or without LIF (page 13729, col. 1-2, bridg. parag). Primordial germ cells (PGC's) are the source for embryonic germ (EG) cells, and in mice is a cell that shares pluripotent characteristics with mouse ES cells (page 13726, col. 1, lines 1-5). Shambloott also teaches that human EG cells have several characteristics in common with mouse ES and EG cells, especially the ability to develop into all three germ layers (page 13726. col. 2, parag. 1 and page 13729, col. 2, parag. 5, lines 1-11).

Bain teaches the production of EB's in suspension by the aggregation of mouse ES cells (page 343, col.2, parag. 2, lines 23-26). EB's were cultured in median comprising retinoic acid (RA) (page). EB's were then dissociated with trypsin and plated on laminin-coated dishes (page 344, col. 1, lines 3-6). The monolayer cells, plated on laminin coated plates, developed into neuron-like cells having neuritic processes (page 347, col. 1, lines 3-4).

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Wobus teaches the production of endodermal cells when mouse ES cells are cultured in the presence of nerve growth factor (NGF) and permitted to form EB's (page 969, lines 2-4).

Therefore at the time of the present invention, it would have been obvious to the ordinary artisan to produce human EB's from human ES cells as taught by Thomson using the methodology of Shamblott, and then following the methodology of Bain for mouse EB's, culture the human EB's in the presence of NGF as taught by Wobus, subsequently dissociate the human EB's and plate the embryonic cells thereby produced on a laminin coated plate to produce a monolayer of embryonic cells to observe neuron-like cells with neuritic processes. Motivation can be found in Thomson teaching that human ES cells will offer insights into developmental events that cannot be studied in a human embryo but which have important consequences in birth defects, infertility and pregnancy loss (page 1146, col. 1, parag. 3, lines 1-6). Additional motivation can be found in Wobus stating the results disclosed establish an experimental cell model to study the effect on differentiation of stem cells (page 970, parag. 2). Thus, at the time of filing, the ordinary artisan would have had sufficient teaching, suggestion and motivation to reach the claimed invention to develop an in vitro system to study the role of NGF on human endodermal cell differentiation from ES cells.

Applicant argues that Reubinoff teaches that techniques used to produce EB's from mouse cells would not produce EB's from human ES cells. Applicant argues that Reubinoff teaches human ES cells did not form EB's using the hanging drop method or as aggregates on bacterial Petri dishes. Applicant argues that Reubinoff states that considerable cell death occurred using these methods. Applicant argues that when human ES cells were cultivated to high density on a feeder layer, there was no consistent pattern of structural organization suggestive of the formation of embryoid bodies as is formed in EB's from mouse ES cells.

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Applicant argues that these results are consistent with results obtained when EB formation was attempted using marmoset and rhesus monkey ES cells. These arguments are not persuasive.

Reubinoﬀ states that when human ES cells were cultivated to a high density that organized EB's failed to form. Likewise, Reubinoﬀ states that the cultivation of clumps of ES cells by either the hanging drop or as aggregates on bacterial plates resulted in cell death. However, there is no discussion as to the EB outcome when lower density cultures were a source of cells. There is also no discussion as to the EB outcome using smaller clumps of cells or single cells. Shamblott oﬀers methods, albeit using human primordial germ cells or their derivatives, to produce EB's that are described as having an organized structure (Shamblott, page 13730, fig. 5). Reubinoﬀ does not provide a cellular concentration that defines "high density." All Reubinoﬀ states is the human ES cells were cultured at a high density for 4-7 weeks, and these cells did not form EB's with structure or the cells died. These teachings do not address a case where less dense cell concentrations or where the cells were not cultured so long. Some experimentation is permitted in 103 especially when a positive teaching is provided as Shamblott. It is noted that applicant's speciﬁcation does not teach the concentration of human ES cells plated to produce EB's (speciﬁcation, page 14, lines 17-19). No other guidance to cell plating number could be found. Also, the results of Shamblott obviate any diﬃculties seen with other primate ES cells.

Applicant argues that human ES cells form embryoid bodies with or without LIF and that this diﬀerence would motivate one to develop new protocols from those used to produce mouse EB's, which develop EB's only in the absence of LIF. This argument is not persuasive.

It is not seen that producing human EB's, that is culture with or without LIF aﬀect a diﬀerentiation protocol. The presence or absence of LIF is not in the claims. Further as

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applicant argued, this phenomenon was known in the art at the time of filing. Both Thomson and Shablott currently cited references acknowledge this effect. Differentiation as claimed is concerned with the embryonic cells isolated from the EB's. As long as you have EB's, the formation, the mouse differentiation protocols would be applicable. Furthermore, the cited references in combination meet the limitations in the claims.

Applicant argues that the examiner is confused about what Thomson teaches.

Applicant argues that ES cells can be tumorigenic if injected into a SCID mouse, but that this is not the only and most prominent feature. Applicant argues that directing differentiation in vitro and having cells differentiate in vivo are completely different.

Applicant argues that the ES cells line obtained by Thomson is not what is described in the present invention. Applicant argues that that Reubinoff's position that human EB's cannot be obtained from human ES cells. Declarant Benvenisty states that the problem his laboratory is trying to solve is the development of stem cell derived differentiated cells lines that can be used for transplantation. Applicant argues that Thomson teaches away from the presently claimed invention. Declarant states that Thomson is even more problematic because the reference only teaches the formation of germ layers in a teratoma, and that these are not differentiated embryonic cells to a specific cell type. Applicant argues that Thomson teaches an ES cells line that forms teratoma are not capable of having differentiation directed, and thus are not suitable for transplantation. Declarant states that Thomson evaluated only two markers on their ES cells, HCG and AFP, and thus Thomson did not unequivocally prove the generation of differentiated cells lines of three germ layers. These arguments are not persuasive.

Thomson was clearly stated to provide teachings regarding the availability of human ES cells. There is no statement in the rejections made in the previous office action that Thomson teaches directed differentiation, and none is implied. What Thomson does not

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teach in a manner teaches away from the claimed invention. The examiner cannot find in Thomson any teaching that the human ES cells disclosed are not capable of directed differentiation. The formation of teratoma is evidence that the human ES cells are totipotent. Reubinoff does not address the present rejection where the EB's are formed by the methods of Shambloott. Thomson states that when human ES cells grow to confluence and undergo spontaneous differentiation, then they expression  $\alpha$ -fetoprotein and hCG. Because Thomson did not analyze for other markers is not evidence that the human ES cells of Thomson are not capable of directed differentiation.

Applicant argues that Shambloott is not appropriate because the origin of EG and ES cells are different, hEG cells cannot be imprinted de novo and they cannot survive passage more than about 20 times. Declarant states that ES cells, unlike EG cells, have an inherent pluripotency unlike other cell lines. Declarant further states that the EB's of Shambloott are not equivalent to EB's derived from human ES cells. Applicant also argues that hEG cells undergo spontaneous differentiation, which teaches away from the presently claimed invention, which requires directed differentiation. These arguments are not persuasive.

Nothing in Shambloott teaches away from the methods of Shambloott to form EB's from human EG's being used to form EB's from human ES cells. Further, applicant has not offered any evidence, other than opinion, that cells derived from Shambloott's EB's cannot be used for directed differentiation. In the absence of growth factors to direct differentiation, cells from EB's undergo spontaneous differentiation. Is applicant stating that their method of producing human EB's causes cells isolated from the EB's not to undergo spontaneous differentiation when grown in the absence of a feeder layer and/or growth factors? Further, Shambloott teaches their EB cells to grow for about 20 times, but there is no discussion in Shambloott that their EB-derived cells cannot divide for longer times or that their EB-derived

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cells cannot undergo directed differentiation. Further, a teaching away means the reference says something will not happen. A teaching away isn't an absence of a teaching.

Applicant argues that Yuen is related to directed differentiation of cells isolated from mouse ES cells. Applicant then queries "so what?" Applicant states obviousness rejections have the same standard of detail as specifications. Applicant argues that they were the first to show how one can direct differentiation in human ES cells derived from human EB's. Applicant argues that efforts to produced human EB's had failed, and efforts with other primate ES cells to make EB's was sporadic. Applicant argues that Yuen teaches the generation of primitive erythroid cell line from mouse ES cells and not human ES cells. Declaration states that Yuen did not show the presence of EB molecular markers. Declaration also states that those skilled in the art that just because a procedure is successful in mice ES cells that it will be successful in human ES cells.

The present claims have no method steps that distinguish them from Yuen. To meet the limitation in applicant's claims, all one needs to make one human EB from human ES cells, and direct their differentiation. Applicant nor declaration have stated on the record that the methodology used by Yuen to produce the primitive erythroid cells taught would never cause the differentiation of human EB-derived cells into the same cell type. The combination of prior art teaches every element of applicant's claim. The references are not anticipatory, but obviousness rejections are still permissible. If applicant or declarant has experimental evidence that the mouse methods would not be effective on human EB-derived cells, then that evidence should be presented. The combination of prior art meets the level of requirements for specifications set forth in MPEP 2164.03. The question that needs to be answered is what about applicant's claims distinguishes them from those of the cited art. Other than human ES cells, there is no difference. Further, the methods of

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Shamblott were the ones cited for use in preparing human EB's and not Yuen. Applicant should argue the rejection as it is set forth.

Applicant argues that there is no reasonable expectation of success. Applicant argues that knowledge in the field at the time of the present invention did not provide evidence that it was possible to form human EB's from human ES cells. Declarant states that at the time of the present invention, it was possible to only form mouse EB's from mouse ES cells. Declarant states that Reubinooff et al and Thomson et al (1995, 1996) each were unable to form human EB's from human ES cells. These arguments are not persuasive.

The rejection includes Shamblott for the method of forming EB's from human ES cells. Evidence is not of record that the methods of Shamblott would not be form EB's when human ES cells were used in place of human PG cells.

Applicant argues that hindsight cannot be used to support an obviousness rejection when the knowledge required to modify the cited references comes from the applicant's own disclosure. Declarant states that it is erroneous to propose that without undue experimentation it would be obvious combine the cited prior art. Declarant argues that if the claimed methods were obvious, then others would have done it. Declarant argues that their laboratory is the only laboratory in the world to develop the technology to generate embryoid bodies. These arguments are not persuasive.

The examiner has not cited anything from the specification in the rejection. Each limitation in the claims has been rejection by a prior reference. Further, some experimentation is permitted in an obviousness rejection. The examiner knows of no authority that states if that level of experimentation is undue or some other level. In addition, the examiner knows of no authority that guides examination practice to find that if no other research group has published, then no one else has found the invention obvious. If this were the standard, then there'd be no obviousness rejection. Being the first to do

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something in and of itself is not a criterion for patentability. Any technology developed by applicant is not in the claims. The claims encompass any and all methods. Jumping ahead, declarant states that the present applicant uses semi-confluent or high-density cultures. These terms are not defined in the specification as to cell numbers nor are the claims so limited.

Applicant argues with regards to Bain et al, that the methods of forming EB's and differentiating EB-derived by Bain are not effective for human ES cells. Declarant states that the techniques and protocols applied for mouse ES cells were not adequate for human ES cells. Declarant further states the establishment of human EB's from human ES cells may be considered a new and not obvious technology. Regarding Wobus, declarant states that Wobus reports the techingques and protocols that applied for mouse ES cells were not adequate for human ES cells. These arguments are not persausive.

Shamblott provides teachings for the production of human EB's from human PGC's. That PGC's are not the same as ES cells is not sufficient to establish that the methodology would not be effective for human ES cells and human EB formation. One would only need to form sufficient human EB's using Shamblott's method to direct differentiation. It is noted that applicant never states that the combination of factors disclosed in Yeun et al, Bain et al or Wobus et al would be ineffective. Shamblott's EB's developed into the three germ layers: endoderm, mesoderm and ectoderm as indicated by marker analysis (page 13729, Table 1). If human PGC's as applicant are more differentiated than human ES cells, and the human PCG's develop EB's that contain cells of all three germ layers, then it would seem that human ES cells, which are less differentiated would also develop into EB's using Shamblott's method. Again, applicant's claims encompass all methods of making EB's, either from human PGC's or mouse ES cells. Thus, all of these methods must be effect for making human EB's.

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Applicant argues that the examiner's interpretation of Reubinoﬀ is incorrect.

Declarant states that Reubinoﬀ states that "manipulations used in our laboratory to produce EB's and multilineage differentiation of mouse ES cells induced death of human ES cells.

Declarant also states that they used the same methodology as Reubinoﬀ but obtained differentiated cells. Declarant attests that he is regarded by those of skill in the field of stem research to be first to produce human EB's from human ES cells, and then to differentiate cells from those EB's into specific cell types. Applicant argues that Reubinoﬀ states that methods for the differentiation of cells derived from mouse EB's do not work in parallel studies. These arguments are not persuasive.

If Reubinoﬀ and applicant used identical methods for producing EB's from human ES cells, then what did applicant do to be so successful. This has not been stated on the record, nor is such apparent from the specification. Further, the cited prior art included Shamblott. There were no arguments presented that the methods of Shamblott would not produce EB's from human ES cells. At paragraph 8, declarant discusses Shamblott but gives not basis for his opinion. Further, declarant offers no evidence that the EB-derived cells of Shamblott are not pluripotent. Shamblott states that they are. Shamblott states that they form EB's and not embryoid body-like structures. Further there is no evidence that Shamblott's cells cannot be differentiated into a specific cell type by the addition of factors.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory

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period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0408. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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